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(54) Title: USE OF CCK-B RECEPTOR ANTAGONISTS FOR THE TREATMENT OF SLEEP DISORDERS

(57) Abstract

The use of CCK-B antagonists for the treatment of sleep disorders.

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USE OF CCK-B RECEPTOR ANTAGONISTS FOR THE TREATMENT OF SLEEP DISORDERS

The present invention relates to the use of CCK-B antagonists for the treatment of sleep disorders.

Cholecystokinins (CCK) and gastrin are structurally related peptides which exist in gastrointestinal tissue and in the central nervous system. Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form, its carboxyl terminal octapeptide, CCK-8 (also a naturally occurring neuropeptide), and 39- and 12-amino acid forms. Gastrin occurs in 34-, 17- and 14- amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH_2 (CCK-4) which is the common structural element shared by both CCK and gastrin.

CCK and gastrin are gastrointestinal hormones and neurotransmitters in the neural and peripheral systems and perform their respective biological roles by binding to particular receptors located at various sites throughout the body. There are at least two subtypes of cholecystokinin receptors termed CCK-A and CCK-B and both are found in the periphery and in the central nervous system.

The CCK-A receptor, commonly referred to as the "peripheral-type" receptor, is primarily found in the pancreas, gallbladder, ileum, pyloric sphincter and on vagal afferent nerve fibers. Type-A CCK receptors are also found in the brain in discrete regions and serve to provide a number of CNS effects. Due to the ability of CCK-8 and Type-A CCK-selective agonists to suppress food intake in several animal species, considerable interest has been generated toward the development of new substances which function as Type-A receptor-selective CCK agonists in order to serve as anorectic agents.

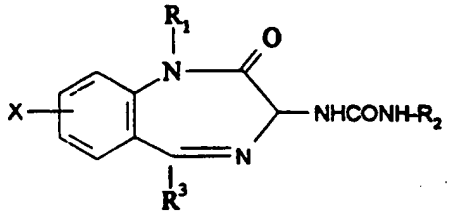
The CCK-B or gastrin receptors are found in peripheral neurons, gastrointestinal smooth muscle and gastrointestinal mucosa, most notably in parietal cells, ECL cells, D cells and chief c lls. CCK-B rec ptors also predominate in the brain and have been implicated in the regulation of anxiety, arousal and the action of neuroleptic agents.

Sleep disorders are the disturbances of sleep that affect the ability to fall and or stay asleep, which involve sleeping too much or result in abnormal behaviour associated with sleep. There are two types of sleep which cyclical and are marked by characteristic electro-encephalograms (EEG) and other changes including eye movements. The first phase of sleep which in normal sleep accounts for 75-80% of total sleep time is referred to as the non-rapid-eye-movement (NREM) type and this is characterised by slow waves on the EEG. The second sleep type (REM-rapid eye movement) which follows NREM is characterised by EEG low voltage fast activity and occurs 5 to 6 times during a normal nights sleep. In sleep disorders the balance of the two types of sleep is disturbed.

We have now found compounds which exhibit an antagonist activity at the CCK-B receptor influence sleep patterns and are therefore useful for the treatment of sleep disorders.

Thus the present invention provides for the use of a compound having an antagonist activity at the CCK-B receptor in the manufacture of a medicament for the treatment of sleep disorders.

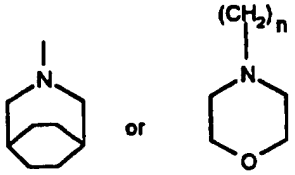
Examples of suitable CCK-B antagonists for use in the treatment of sleep disorders includes the 1,4-benzodiazepine derivatives having CCK-B antagonist activity described in EPA 167919, EPA 284256, EPA 434360, EPA 434364, EPA 434369, EPA 514125, EPA 51426, EPA 514133, EPA 508796, EPA 508797, EPA 508798, EPA 508799, EPA 523845, EPA 523846, EPA 559170, EPA 549039, WO 9211246, WO 93032078, WO 9308175, WO 9307131, WO 9317011, WO 9319053, WO 9308175, WO 9413648 WO 9403437. The subject matter of the above identified published patent applications are incorporated herein by reference. Within the 1,4 benzodiazepine derivative disclosed above a particularly useful class of CCK-B antagonists include representated by the general formula (I).



(I)

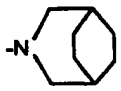
and N-oxides thereof and pharmaceutically acceptable salts thereof
wherein R_1 represents C_{1-6} alkyl (optionally substituted by hydroxyl C_{1-4} alkoxy, COR_4, $CONR_5R_6$ or C_{3-7} cycloalkyl) or C_{3-7} cycloalkyl;
R_4 represents C_{1-6} alkoxy or optionally substituted phenyl;
R_6 is methyl or ethyl and R_6 is phenyl or R_5 and R_6 together form a C_4-C_6 alkylene chain, which may be substitued by 1 or 2 alkyl groups;
R_2 represents a substituted or unsubstituted phenyl group (wherein the substitutents may be 1 or 2 of halo, C_{1-4} alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkylthio or $(CH_2)n$ R_7 wherein R_7 is hydroxy, C_{1-4} alkoxy, CO_2R_8, NR_8R_9, $SO_2NR_8COR_{10}$, $CONR_8SO_2R_{10}$, or R_7 represents a tetrazolyl, carboxamidotetrazolyl, 3-trifluoromethyl-1,2-4-triazolyl or 5-oxo-1,2,4 oxadiazolyl group, which groups may be substituted on one of the nitrogen atoms by a C_{1-4}alkyl group;
R_8 represents hydrogen of a C_{1-4}alkyl group;
R_9 independently represents hydrogen or a C_{1-4}alkyl group or the group SO_2CF_3;
R_{10} represents C_{1-4}alkyl;
R_3 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl (optionally substituted by halogen), azacycloalkyl or alkyl substituted by an amino, C_{1-4} alkylamino, diC_{1-4}alkylamino, morpholino, pyrrolidino, piperidino, hexamethylene, thiomorpholino or N-methyl piperazino group; X represents hydrogen or halogen.

Within this class particularly preferred compounds include those wherein R_1 is alkyl e.g. methyl, isopropyl or CH_2COR_4 wherein R^4 is optionally substituted phenyl or the group CH_2CO NR_5R_6 wherein R_5 is methyl or ethyl and R_6 is an optionally substituted phenyl group or NR_5R_6 represents a pyrrolidino, or piperidino group, which groups may be optionally substituted by on or 2 alkyl groups;
and R_3 is alkyl, cycloalkyl, phenyl optionally substitut d by fluorin or a group s l ct d from



or wherein n is 1 or 2

Examples of particularly suitable compounds from within this class are those wherein X is hydrogen, and R_1 is methyl, R_3 is phenyl and R_2 is 3-methyl phenyl or 3-(5-oxo-1,2,4-oxadiazol-3-yl) phenyl or R_1 is methyl, R_2 is 3-methyl phenyl and R_3 is



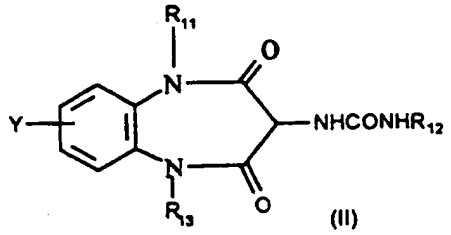
or R_1 is isopropyl, R_3 is phenyl and R_2 is 3-(1H-tetrazol-5-yl) phenyl.

or R_1 is CH_2COR_4 wherein R_4 is 2-methylphenyl, R_2 is 3 methylphenyl and R_3 is phenyl

Further examples of suitable CCK-B antagonists for use in the invention include the 1,5-benzodiazepine derivatives having CCK-B antagonist activity described in WO9314074, WO9314075, WO94261491, WO9424151, WO9425444, WO9503299, WO9503284, WO9503285 and WO9425445.

The subject matter of the above identified patent applications is incorporated herein by reference.

Within the 1,5-benzodiazepine derivatives described in the above identified patent applications a particularly useful class of CCK-B antagonists for use in this invention are those of general formula (II).



(II)

wh r in

R_{11} represents a phenyl, C_{3-7}cycloalkyl, C_{7-11} bridgedcycloalkyl or C_{1-6}alkyl group which alkyl group may be substituted by a hydroxy, phenyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, or C_{7-11} bridgedcycloalkyl group;
R_{12} represents a phenyl group optionally substituted by 1 or 2 substituents selected from, halogen, C_{1-4}alkyl, C_{1-4}alkylthio, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(CH_2)nR_{14}$ or $O(CH_2)pR_{14}$ wherein R_{14} represents hydroxy, C_{1-4}alkoxy, CO_2R_{15} or $NR_{16}R_{17}$; n is zero or 1; p is an integer from 1 to 4;
R_{13} represents the group $AlkNR_{18}R_{19}$ or phenyl optionally substituted by 1 or 2 halogen atom;
R_{15} represents hydrogen or C_{1-4}alkyl;
R_{16} represents hydrogen or C_{1-4}alkyl;
R_{17} represents hydrogen, C_{1-4}alkyl, acyl, or C_{2-6}alkyl substituted by one or more hydroxy, carboxyl and/or amino groups or R_{16} and R_{17} together with the nitrogen atom to which they are attached form a 5-7 saturated heterocyclic ring which contain an additional heteroatom selected from oxygen, sulphur or nitrogen and/or may be substituted by 1 or 2 C_{1-4}alkyl or hydroxy groups.
R_{18} and R_{19} independently represent hydrogen, C_{1-4}alkyl or C_{2-6}alkyl substituted by one or more hydroxy, carboxyl and/or amino groups or R_{18} and R_{19} together with the nitrogen atom to which they are attached represent a 5-7 saturated heterocyclic ring which may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and/or may be substituted by 1 or 2 C_{1-4}alkyl or hydroxy groups; Alk represents a straight or branched C_{2-6}alkylene chain optionally substituted by an hydroxyl group;
Y represents hydrogen or 1 or 2 halogen atoms;
and pharmaceutically acceptable salts and or metabolically labile esters.

For compounds of formula (II) examples of suitable R_{11} groups include a C_{4-6}alkyl e.g. 3-methyl butyl, 3,3-dimethyl butyl, C_{3-6} hydroxy alkyl e.g. 2-hydroxypropyl, 2-hydroxy-3- methylbutyl, 2-hydroxy-3,3-dimethylbutyl, C_{1-2}alkyl substituted by a bridged C_{7-10}cycloalkyl group e.g. 2-norbornanylmethyl, 5-norbornenylmethyl, 1-adamantylmethyl, alkoxycarbonylalkyl, e.g. methoxycarbonylmethyl or t-butyoxycarbonylmethyl, cyclohexylmethyl, or 2-cyclopentylethyl.

Conveniently R_1 represents 3-methylbutyl or 1-adamantylmethyl and mor particularly 1-adamantylmethyl.

When R_{13} is an optionally substituted phenyl group this is conveniently phenyl or 2-fluorophenyl and more particularly phenyl.

When R_{13} is the group $AlkNR_{18}R_{19}$; the group Alk conveniently represents ethylene, propylene or 2-hydroxymethyl-ethylene and more particularly ethylene.

Examples of suitable $NR_{18}R_{19}$ groups include amino, dimethylamino, diethylamino, morpholino, pyrrolidino, piperidino or hexamethyleneimino.

Conveniently R_{13} represents morpholinoethyl, piperidinoethyl, pyrrolidinoethyl, dimethylaminoethyl, diethylaminoethyl, dimethylamino-propyl or 2-hydroxymethyl-2-aminoethyl or hexamethyleneiminoethyl. More preferably R_{13} represents morpholinoethyl.

Y conveniently represents fluorine or chlorine or more particularly hydrogen.

A preferred group of compounds of formula (II) for use in the invention are those wherein R_{11} represents 1-adamantylmethyl R_{12} is phenyl optionally substituted in the meta position by a methyl, methoxy, methylthio, nitro, dimethylamino, ethoxycarbonyl or carbonyl group; R_{13} is phenyl and Y is hydrogen. Within this group especially preferred compounds are those wherein R_{12} is phenyl optionally substituted by dimethylamino, ethoxycarbonyl or carboxyl group.

A further preferred group of compounds of formula (II) for use in the present invention include those wherein R_{11} is 1-adamantylmethyl, R_{12} is phenyl optionally substituted by halogen e.g. fluorine or bromine, R_{13} represents, 2-(4-morpholino)ethyl, 2-(1-piperidino)ethyl, 2-(1-pyrrolidino)ethyl, 2-(dimethylamino)ethyl, 3-(dimethylamino)propyl, 2-hydroxymethyl -2-aminoethyl, 3-aminopropyl, and Y is hydrogen or fluorine.

A yet further preferred group of compounds of formula (II) for use in the present invention include those wherein R_{11} is 3-methylbutyl, R_{12} is phenyl optionally substituted by methyl, methoxy, chlorine, bromine, fluorine, trifluoromethyl,

hydroxy or methoxy, R_{13} is 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 2-(1-piperidino)ethyl or 2-(4-morpholino)ethyl, Y is hydrogen or fluorine.

A further preferred group of compounds of formula (II) are those wherein R_{11} is 1-adamantylmethyl, R_{13} is phenyl or the fluorophenyl and R_{12} is phenyl or phenyl substituted by methyl, methoxy, methylthio, nitro, dimethylamino, ethoxycarbonyl or carboxy or R_{13} represents 2-(4-morpholino)ethyl, 2-(1-piperidino)ethyl, 2-(1-pyrrolidino)ethyl, 2-(dimethylamino)ethyl, 3-(dimethylamino)propyl, 2-hydroxymethyl -2-aminoethyl, 3-aminopropyl, R_{12} is phenyl or phenyl substituted by methyl, methoxy or flourine, Y is hydrogen or fluorine, and more particularly hydrogen.

Specific preferred compounds of formula (II) for the treatment of sleep disorders include the specific preferred compounds described in WO9314074, WO9503285 and WO9503284.

Particularly preferred compounds of formula (II) for use in the treatment of sleep disorders include:

N-phenyl-N'-[2,3,4,5-tetrahydro-2,4-dioxo-1-(1-adamantylmethyl)-5-phenyl-1H-1,5-benzodiazepin-3-yl]urea;

N-[1-(1-Adamantylmethyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-benzodiazepin-3-yl]-N'-phenylurea;

N-1[-(Adamantylmethyl)-2,4,-dioxo-5-phenyl-2,3,4,5-tetrahydro-1 H-1,5-benzodiazepin-3-yl]-N'-(3-carboxyphenyl)urea;

N-[(1-Adamantylmethyl)-5-[2-(dimethylamino)ethyl]-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea;

and enantiomers and physiologically acceptable salts th reof.

It will b appreciated that compounds of formula (I) and (11) poss ss at least n asymmetric carbon atom (namely th carbon atom occupying the 3-position of the

diazepine ring) and the compounds of the invention thus include all stereoisomers and mixtures thereof including the racemates.

Further examples of CCK-B antagonists for use in the invention include the peptide derivatives described in EPA 4055537, WO 9204045, WO 9204322, WO9204348 WO 91/3907 and EPA all of which by way of reference are incorporated herein

Conveniently the peptide derivatives with CCK-B antagonist activity for use in the invention include the tryptophan based dipeptoids and in particular;

[1S-[1α,2β,[S*(S*)],4α]-4-[[2-[[3-(1H-3-yl)-2-methy1-1-oxo-2-[[[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl) oxy]carbonyl]amino]propyl]amino]-1-phenylethyl]amino]-4-oxobutanoic acid and salts thereof and

(R-(R*,R*))-4-((2-((3-(1H-indol-3-yl)-2-methyl-2-((tricyclo(3.3.1.1,3,7)dec-2-yloxy)carbonyl)amino)propyl) amino)-1-phenylethyl)amino)-4-oxobutanoic acid and salts thereof.

Yet further examples of CCK-B agonists for use in the treatment of sleep disorders include those described in WO9507261, WO9503281, EP620221, WO9419322, WO9400421, WO9401421, WO9315059, WO9321172, EP518731, WO9210479, USP53997308, EP655053, WO9505359, WO9419322, WO9406802, WO9426718, WO9294045 and EP46714.

From within the compounds described therein particularly useful compounds include the 3-phenylureido-azepin-2-ones and 3-phenylureido-benzazepin-2-ones described in WO9315059 and which are incorporated herein by way of reference. From within this class a particularly interesting compound is N-tert butyl 2[3-[3-(3-chlorophenyl)ureido]-2-oxo-5-phenyl-4,3,4,5-tetrahydro-1H-(1)-benzazepin-1-yr]ethanoic acid amide.

A further interesting class CCK-B antagonist for use in the inv ntion are th aspartic acid and glutamic acid derivatives described in WO9210479 and WO9507261. Examples of particularly suitable compounds from within this class are spiroglumide and related compounds.

Preferred CCK-B antagonist for use in the treatment of sleep disorders include.

(a) 1,4-benzodiazepines of formula (I) and more particularly the compounds wherein X is hydrogen, R_1 is methyl, R_2 is 3-methylphenyl or 3-(5 oxo-1,2,4-oxadiazol-3-yl) phenyl and R_3 is phenyl; X is hydrogen. R_1 is methyl, R_2 is 3 methylphenyl and R_3 is 3-azabicyclo-[3.3.1]nonan-3-yl, X is hydrogen, R1 is CH_2COR_4 wherein R_4 is 2-methylphenyl, R_2 is 3-methylphenyl and R_3 is phenyl or X is hydrogen, R_1 is isopropyl, R_3 is phenyl and R_2 is 3 (1H-tetrazol-5-yl) phenyl.

(b) 1,5 benzadiazepines of formula (II) and more particularly the compounds.

N-phenyl-N'-[2,3,4,5-tetrahydro-2,4-dioxo-1-(1-adamantylmethyl)-5-phenyl-1H-1,5-benzodiazepin-3-yl]urea;

N-[1-(1-Adamantylmethyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-benzodiazepin-3-yl]-N'-phenylurea;

N-1[-(Adamantylmethyl)-2,4,-dioxo-5-phenyl-2,3,4,5-tetrahydro-1 H-1,5-benzodiazepin-3-yl]-N'-(3-carboxyphenyl)urea;

N-[(1-Adamantylmethyl)-5-[2-(dimethylamino)ethyl]-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea;

(c) the tryptophan peptide derivatives.

[1S-[1α,2β,[S*(S*)],4α]-4-[[2-[[3-(1H-3-yl)-2-methy1-1-oxo-2-[[[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl) oxy]carbonyl]amino]propyl]amino]-1-phenylethyl]amino]-4-oxobutanoic acid and salts thereof and

(R-(R*,R*))-4-((2-((3-(1H-indol-3-yl)-2-methyl-2-((tricyclo(3.3.1.1,3,7)dec-2-yloxy)carbonyl)amino)propyl) amino)-1-ph nyl thyl)amino)-4-oxobutanoic acid and salts th reof;

(d) N-tert butyl-2-[3[3-(3-chlorophenyl)ureido-2-oxo-5-phenyl-2,3,4,5 tetrahydro-1H-(1)-benzazepin-1-yl]ethanoic acid amide.

(e) (R)-γ(3,5-dichloro-benzamido]δ-oxo-8-azaspiro[4,5]decane-8-valeric acid (spiroglumide).

References hereinafter to a CCK-B antagonists (I) also includes where appropriate pharmaceutically acceptable salts and or solvates thereof.

Particularly useful CCK-B antagonists for use in the treatment of sleep disorders are:

(+) N-phenyl-N'-[2,3,4,5-tetrahydro-2,4-dioxo-1-(1-adamantylmethyl)-5-phenyl-1H-1,5-benzodiazepin-3-yl]urea (compound 1);

(-) N-[1-(1-Adamantylmethyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-benzodiazepin-3-yl]-N'-phenylurea (compound 2);

N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N'-3-methylphenyl urea (compound 3);

(R-(R*,R*))4-((2-((3-(1H-indol-3-yl)-2-methyl-2-((tricyclo(3,3,1,1,3,7)dec-2yloxy)carbonyl)amino propyl)amino)-1-phenylethyl)amino-4-oxo-butanoic acid meglumine salt (compound 4).

N-1[-(Adamantylmethyl)-2,4,-dioxo-5-phenyl-2,3,4,5-tetrahydro-1 H-1,5-benzodiazepin-3-yl]-N'-(3-carboxyphenyl)urea (compound 5);

N-[(1-Adamantylmethyl)-5-[2-(dimethylamino)ethyl]-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea (compound 6);

Th ability of the compounds which exhibit CCK-B antagonist activity to influence sleep patt rns may b d monstrated by xamining EEG parameters in old rats. In these animals the EEG patterns are disturbed. Administration of an ffective amount of a CCK-B antagonist to such an animal alt rs the EEG patt rn

towards the normal. These effects may be observed using standard procedures such as those described by H.Depoortere et al. Physiology & Behaviour 1993, 54, 785-793.

Thus CCK-B antagonists may be useful for the treatment of sleep disorders, including Disorders of Initiating and Maintaining Sleep (insomnias), (DIMS) which can arise from psychophysiological causes, as a consequence of psychiatric disorders (particularly related to anxiety), from drugs and alcohol use and abuse (particularly during withdrawal stages), childhood onset DIMS, nocturnal myoclonus and restless legs and non specific REM disturbance as seen in ageing. Disorders of the Sleep-Wake Schedule which include jet-lag, disorder due to shift work, delayed sleep phase syndrome, advanced sleep phase syndrome, non-24h sleep phase syndrome, disorders due to blindness and those caused by ageing and dementias. Dysfunctions associated with sleep (parasomnias) for example sleep related enuresis.

According to a further aspect of the invention we provide a method for the treatment of mammal, including man, for sleep disorders which method comprises administering an effective amount of a CCK-B antagonist or a pharmaceutically acceptable salt or solvate thereof to the patient.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of the CCK-B antagonist required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 0.01-2000mg per day e.g 0.01-500mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, thr e, four or mor sub-doses per day.

While it is possible that, for use in therapy, the CCK-B antagonist may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation for the treatment of sleep disorders comprising a CCK-B antagonist or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, implant, or rectal administration. Oral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, accacia, gelatin, sorbitol, tragacanth, hydroxypropyl cellulose, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, hydrogenated vegetable oils, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compositions may also be formulated as suppositories, .g.

containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in prefilled syringes, vials and ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form which may be obtained by freeze drying for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The composition according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compositions according to the invention may contain between 0.1 - 99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

Examples of suitable pharmaceutical formulations for use in the treatment of sleep disorders include those already specifically described in the specifications of the patent applications referred to above and incorporated hereinto by reference.

For administration in the form of a tablet a convenient formulation is as follows:

Ingredient	mg/tab
CCK-B antagonist	1.00
Povidone K-30	0.11
Microcrystalline Cellulose	142.44
Croscarmellose sodium	6.00
Magnesium Stearate	0.45
Compression weight	150.00mg

The CCK-B antagonist and Povidone are dissolved in a suitable solvent such as a mixture of acetone and methanol and the resultant solution spray dried using conventional equipment. The resulting powder is blended with the remaining excipients and compressed using 7.5mm normal concave looking. The tablets are coated using conventional methods and equipment. An example of a suitable coating material is Opadry white OY-S-7322 (Colorcon). The above formulation is particularly convenient for use with the CCK-B antagonist - Compound 1.

Pharmacological Activity

The ability of CCK-B antagonists to effect sleep patterns in old rats was measured by examining the effect of the compound on the EEG pattern using the procedures described by H Depoortere et al. Physiology & Behaviour 1993 54, 785-793. In this test it was found that a single dose i.p. or p.o. of the CCK-B antagonist resulted in an improvement in total sleep time, in both NREM and REM together with being less awake and with a shorter awakening duration. Thus doses of compounds 1 to 6 identified above that resulted in a significant improvement in total sleep time pattern are as follows:

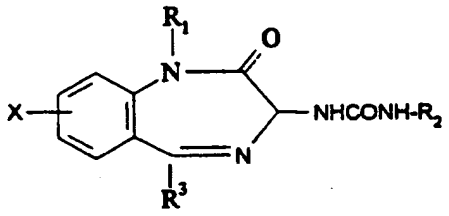
CCK-B Antagonist	Dose
Compound 1	5 µg/kg ip and po
Compound 2	0.5µg/kg ip
Compound 3	5 µg/kg ip
Compound 4	5 µg/kg ip
Compound 5	15 µg/kg ip
Compound 6	0.5 µg/kg ip

Claims

1. The use of a compound having an antagonist activity at the CCK-B receptor in the manufacture of a medicament for the treatment of sleep disorders.

2. Use according to claim 1 wherein the CCK-B receptor antagonist is a 1,4-benzodiazepine derivative, a 1,5-benzodiazepine derivative, a peptide derivative, a 3-phenylureido-azepen-2-one or 3-phenylureido-benzazepin-2-one derivative or an aspartic acid or glutamic acid derivative.

3. Use according to claim 1 or 2 wherein the CCK-B receptor antagonists is a 1,4 benzodiazepine derivative of formula (I).



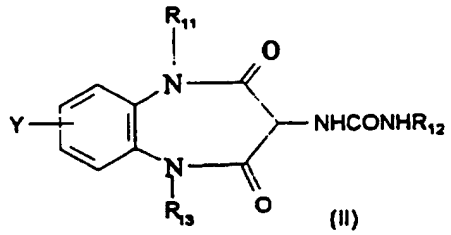
(I)

and N-oxides thereof and pharmaceutically acceptable salts thereof
wherein R_1 represents C_{1-6} alkyl (optionally substituted by hydroxyl C_{1-4} alkoxy, COR_4, $CONR_5R_6$ or C_{3-7} cycloalkyl) or C_{3-7} cycloalkyl;
R_4 represents C_{1-6} alkoxy or optionally substituted phenyl;
R_6 is methyl or ethyl and R_5 is phenyl or R_5 and R_6 together form a C_4-C_6 alkylene chain, which may be substitued by 1 or 2 alkyl groups;
R_2 represents a substituted or unsubstituted phenyl group (wherein the substitutents may be 1 or 2 of halo, C_{1-4} alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkylthio or $(CH_2)n$ R_7 wherein R_7 is hydroxy, C_{1-4} alkoxy, CO_2R_8, NR_8R_9, $SO_2NR_8COR_{10}$, $CONR_8SO_2R_{10}$, or R_7 represents a tetrazolyl, carboxamidotetrazolyl, 3-trifluoromethyl-1,2-4-triazolyl or 5-oxo-1,2,4 oxadiazolyl group, which groups may be substituted on one of the nitrogen atoms by a C_{1-4}alkyl group;
R_8 represents hydrogen of a C_{1-4}alkyl group;
R_9 independently represents hydrogen or a C_{1-4}alkyl group or the group SO_2CF_3;
R_{10} r pr sents C_{1-4}alkyl;

R_3 r presents C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl (optionally substitut d by halogen), azacycloalkyl or alkyl substituted by an amino, C_{1-4} alkylamin , diC_{1-4}alkylamino; morpholino, pyrrolidino, piperidino, hexamethylene, thiomorpholino or N-methyl piperazino group; X represents hydrogen or halogen.

4. Use according to claims 1 to 3 wherein the CCK-B antagonist is a 1,4-benzodiazepine derivative of formula (I) wherein X is hydrogen, R_1 is methyl, R_2 is 3-methylphenyl or 3-(5 oxo-1,2,4-oxadiazol-3-yl) phenyl and R_3 is phenyl; X is hydrogen. R_1 is methyl, R_2 is 3 methylphenyl and R_3 is 3-azabicyclo-[3.3.1]nonan-3-yl, X is hydrogen, R1 is CH_2COR_4 wherein R_4 is 2-methylphenyl, R_2 is 3-methylphenyl and R_3 is phenyl or X is hydrogen, R_1 is isopropyl, R_3 is phenyl and R_2 is 3 (1H-tetrazol-5-yl) phenyl.

5. Use according to claims 1 or 2 wherein the CCK-B antagonists is a 1,5 benzodiazepine derivative of formula (II)



(II)

5.

wherein

R_{11} represents a phenyl, C_{3-7}cycloalkyl, C_{7-11} bridgedcycloalkyl or C_{1-6}alkyl group which alkyl group may be substituted by a hydroxy, phenyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, or C_{7-11} bridgedcycloalkyl group;

R_{12} represents a phenyl group optionally substituted by 1 or 2 substituents selected from, halogen, C_{1-4}alkyl, C_{1-4}alkylthio, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(CH_2)nR_{14}$ or $O(CH_2)pR_{14}$ wherein R_{14} represents hydroxy, C_{1-4}alkoxy, CO_2R_{15} or $NR_{16}R_{17}$; n is zero or 1; p is an integer from 1 to 4;

R_{13} represents the group Alk$NR_{18}R_{19}$ or phenyl optionally substituted by 1 or 2 halogen atom;

R_{15} represents hydrogen or C_{1-4}alkyl;

R_{16} represents hydrogen or C_{1-4}alkyl;

R_{17} represents hydrogen, C_{1-4}alkyl, acyl, or C_{2-6}alkyl substituted by one or mor hydroxy, carboxyl and/or amino groups or R_{16} and R_{17} togeth r

with the nitrogen atom to which they ar attached form a 5-7 saturat d heterocyclic ring which contain an additional heteroatom selected from oxygen, sulphur:or nitrogen and/or may be substituted by 1 or 2 C_{1-4}alkyl or hydroxy groups.

R_{18} and R_{19} independently represent hydrogen, C_{1-4}alkyl or C_{2-6}alkyl substituted by one or more hydroxy, carboxyl and/or amino groups or R_{18} and R_{19} together with the nitrogen atom to which they are attached represent a 5-7 saturated heterocyclic ring which may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and/or may be substituted by 1 or 2 C_{1-4}alkyl or hydroxy groups; Alk represents a straight or branched C_{2-6}alkylene chain optionally substituted by an hydroxyl group;

Y represents hydrogen or 1 or 2 halogen atoms;

and pharmaceutically acceptable salts and or metabolically labile esters.

6. Use according to claim 5 wherein the CCK-B antagonist is a compound selected from:

N-phenyl-N'-[2,3,4,5-tetrahydro-2,4-dioxo-1-(1-adamantylmethyl)-5-phenyl-1H-1,5-benzodiazepin-3-yl]urea;

N-[1-(1-Adamantylmethyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-benzodiazepin-3-yl]-N'-phenylurea;

N-1[-(Adamantylmethyl)-2,4,-dioxo-5-phenyl-2,3,4,5-tetrahydro-1 H-1,5-benzodiazepin-3-yl]-N'-(3-carboxyphenyl)urea;

N-[(1-Adamantylmethyl)-5-[2-(dimethylamino)ethyl]-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea;

and enantiomers thereof.

7. Use according to claims 1 or 2 wherein the CCK antagonists is a peptide derivative selected from'

[1S-[1α,2β,[S*(S*)],4α]-4-[[2-[[3-(1H-3-yl)-2-methy1-1-oxo-2-[[[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl) oxy]carbonyl]amino]propyl]amino]-1-ph nyl thyl]amino]-4-oxobutanoic acid and salts th reof and

(R-(R*,R*))-4-((2-((3-(1H-indol-3-yl)-2-methyl-2-((tricyclo(3.3.1.1,3,7)dec-2-yloxy)carbonyl)amino)propyl) amino)-1-phenylethyl)amino)-4-oxobutanoic acid and salts thereof;

8. Use according to claims 1 or 2 wherein the CCK-B antagonist is N-tert butyl-2-[3[3-(3-chlorophenyl)ureido-2-oxo-5-phenyl-2,3,4,5 tetrahydro-1H-(1)-benzazepin-1-yl]ethanoic acid amide.

9. Use according to claims 1 or 2 wherein the CCK-B antagonist is (R)-γ(3,5-dichloro-benzamido]δ-oxo-8-azaspiro[4,5]decane-8-valeric acid.

10. The use of (+) N-phenyl-N'-[2,3,4,5-tetrahydro-2,4-dioxo-1-(1-adamantylmethyl)-5-phenyl-1H-1,5-benzodiazepin-3-yl]urea in the manufacture of a medicament for the treatment of sleep disorders.

11. The use of a compound selected from;

(-) N-[1-(1-Adamantylmethyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-benzodiazepin-3-yl]-N'-phenylurea;

N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N'-3-methylphenyl urea;

(R-(R*,R*))4-((2-((3-(1H-indol-3-yl)-2-methyl-2-((tricyclo(3,3,1,1,3,7)dec-2yloxy)carbonyl)amino propyl)amino)-1-phenylethyl)amino-4-oxo-butanoic acid meglumine salt;

N-1[-(Adamantylmethyl)-2,4,-dioxo-5-phenyl-2,3,4,5-tetrahydro-1 H-1,5-benzodiazepin-3-yl]-N'-(3-carboxyphenyl)urea;

N-[(1-Adamantylmethyl)-5-[2-(dimethylamino)ethyl]-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea;

for the treatment of sleep disorders.

12. A method for the treatment for sleep disorders which comprises administering an effectiv amount of a CCK-B antagonist or a pharmaceutically acceptable salt th reof to the patient.

INTERNATIONAL SEARCH REPORT

Int'nal Application No
PCT/EP 95/04024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/55 A61K31/405 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 15059 (PFIZER INC.) 5 August 1993 cited in the application see the whole document especially page 122, line 5-6; ---	1,2,8,12
A	EP,A,0 558 104 (GLAXO SPA) 1 September 1993 cited in the application see the whole document ---	1,2,5,6, 10-12
A	INT. J. CLIN. PHARMACOL. RES., 1993, 13/6 (331-344), SWITZERLAND, MOSCONI M. ET AL 'New anxiolytics in development' see page 335, right column, line 32 - page 338, left column, line 16 ---	1-4,7, 11,12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 1996	23.02.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. nal Application No
PCT/EP 95/04024

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. PHARMACOL. EXP. THER., 1994, 269/2 (725-731), USA, NISHIDA A. ET AL 'Pharmacological profile of (R)-1-(2,3-dihydro-1-(2'-methylphenacyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-3-(3-methylphenyl)urea (YM022), a new potent and selective gastrin/cholecystokinin-B receptor antagonist, in vitro and in vivo' see the whole document ---	1-4,11, 12
A	DRUGS FUTURE, 1993, 18/10 (919-931), SPAIN, MAKOVEC F. 'CCK-B/gastrin-receptor antagonists' see the whole document -----	1-3,7,9, 11,12

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

National application No.
PCT/EP 95/04024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see annex!

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please see annex!

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FR M PCT/ISA/210

The expression "a compound having antagonist activity at the CCK-B receptor" is not a clear and limited description of a chemical compound because it leaves the structural nature of the molecule open. A compound cannnot be defined in terms of its putative biological activity. Because of the use of this open-ended expression a complete search would involve a major part of the chemistry related IPC documentation. Such a search is economically not feasible.

Furthermore, in view of the large number of compounds which are theoretically defined by the Markush formulae of claims 3 & 5 and in the description the search had to be restricted on economic grounds and was directed towards the specifically claimed compounds and the general inventive concept.

Although Claim 12 is directed towards a method of treatment of the human or animal body the search has been carried out and based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

.ormation on patent family members

Inter al Application No
PC /EP 95/04024

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9315059	05-08-93	AU-B-	3276193	01-09-93
		CA-A-	2117367	05-08-93
		CN-A-	1074903	04-08-93
		CZ-A-	9203910	19-01-94
		EP-A-	0625145	23-11-94
		FI-A-	943513	26-07-94
		HU-A-	70496	30-10-95
		JP-T-	7503465	13-04-95
		NO-A-	942775	20-09-94
EP-A-558104	01-09-93	AP-A-	369	06-11-94
		AU-B-	661749	03-08-95
		AU-B-	3193593	22-07-93
		AU-B-	3450193	03-08-93
		BG-A-	98881	31-03-95
		CA-A-	2087672	22-07-93
		CN-A-	1074678	28-07-93
		CZ-A-	9401736	13-09-95
		WO-A-	9314074	22-07-93
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		HU-A-	67375	28-03-95
		JP-A-	7118244	09-05-95
		NO-A-	942720	20-07-94
		NZ-A-	245715	26-07-95
		SK-A-	86494	08-03-95
		ZA-A-	9300375	18-07-94